Letter to the Editor

Delayed hypersensitivity reactions caused by iodixanol: An assessment of cross-reactivity in 22 patients

To the Editor:

More than 70 million iodinated contrast media (ICM) injections are performed worldwide each year.[1] Delayed hypersensitivity reactions (time to onset between 1 hour and 1 week)[2] to iodixanol occurred in approximately 0.4% of the patients,[3] which is fewer than the average incidence of delayed hypersensitivity reactions to ICM in general (reported in 1% to 3% of the patients).[1] Delayed hypersensitivity reactions to iodixanol mainly consist of maculopapular exanthemas without involvement of other organs.[4] Skin tests in investigating delayed reactions to ICM have been considered to have a low negative predictive value, and their diagnostic value appears to be insufficient.[5]

We retrospectively analyzed 22 cases of delayed hypersensitivity reactions subsequent to an intravascular iodixanol injection. Seven women and 15 men with a mean age of 56 ± 14 years (8-78 years) were evaluated. In our study reactions occurred within 10 hours to 6 days after intravenous administration of ICM; the time to the onset of the reaction was less than 3 days in more than 80% of the patients (Fig 1), which is in accord with a previous publication.[6] Reaction duration was 24 hours to 3 weeks. Twenty (90.9%) patients exhibited a maculopapular exanthema with predominant involvement of the trunk; in some the rash extended to the proximal limbs or the face. Facial edema was reported in 2 cases. All patients recovered without sequelae. Two patients experienced delayed reactions despite an immunosuppressive treatment prescribed for prevention of graft rejection (cyclosporine and corticosteroids, patients 13 and 14).

Skin tests were performed in accordance with European Network of Drug Allergy/European Academy of Allergology and Clinical Immunology recommendations[7] by using iodixanol (Visipaque; Amersham Health, Vélizy, France), iobitridol (Xenetix; Guerbet, Roissy-Charles-De-Gaulle, France), iohexol (Omnipaque; GE Healthcare, Vélizy, France), iomeprol (Iomeron; Altana Pharma, Le Mée-sur-Seine, France), iopamidol (Iopamiron; Schering, Lys-Lez-Lannoy, France), sodium meglumine ioxaglate (Hexabrix, Guerbet), and meglumine ioxitalamate (Telebrix, Guerbet). Some patients (patients 1-13 and 15-18) underwent additional skin tests with sodium meglumine amidotrizoate (Radioselectan, Schering), iopentol (Ivepaque, Amersham Health), iopromide (Ultravist, Schering), and ioversol (Optiray, Guerbet); patient 14 had additional skin tests with iopentol and ioversol. Skin prick tests were carried out on the volar surface of the forearm, and a wheal diameter of greater than 3 mm compared with the negative control (saline) at 20 minutes was considered a positive immediate response. Intradermal tests (IDTs) were performed on the back by injecting 0.02 mL of ICM to obtain a wheal size of 3 to 4 mm in diameter. An increase in diameter of greater than 3 mm at 20 minutes was considered a positive response.[7] The IDT results were considered positive on delayed readings if an erythematous indurated papule was observed 24 hours later. If skin prick test responses with undiluted ICM were negative, then IDTs were placed at increasing concentrations, beginning at a 10^{-3} dilution and gradually increasing until the undiluted ICM was reached. In instances of negative immediate skin test results (reading at 20 minutes), patch tests were performed with undiluted ICM, and the results were read according to an internationally accepted method. Delayed readings were done at 24 hours, 48 hours, and, in some cases, 72 hours, 96 hours, or both. Twenty control subjects who had previously undergone ICM-based examination without adverse reactions were included. All of them had negative skin prick, intradermal, and patch test results.

An alternative ICM to which the patient had a negative skin test result was recommended to radiologists if additional ICM-based examination was required.

All patients had negative immediate skin test results. Delayed skin test results with iodixanol were positive in 11 (50.0%) of 22 patients; 8 patients had positive IDT results, 1 had positive patch test results, and 2 others had both delayed positive IDT and patch test results (Table I). Although they were receiving immunosuppressive therapy, skin test results were positive in patients 13 (IDT and patch test) and 14 (IDT). Cross-reactivity to ionic, nonionic, or both types of ICM was detected in 7 cases; iohexol, the monomer of iodixanol, was the most frequent cross-reacting ICM (6 cases), followed by ioversol (4 cases); iopentol (3 cases); iomeprol, iopamidol, and ioxitalamate (2 cases each); and amidotrizoate, iobitridol, and ioxaglate (1 case each). Twenty-two patients were successfully challenged with another ICM (full-dose challenge) that yielded negative skin test results (Table II).[8]

In summary, skin testing (IDTs and patch tests) was useful in implicating iodixanol as the cause of a delayed hypersensitivity reaction in our patients. Skin testing with a panel of different ICM

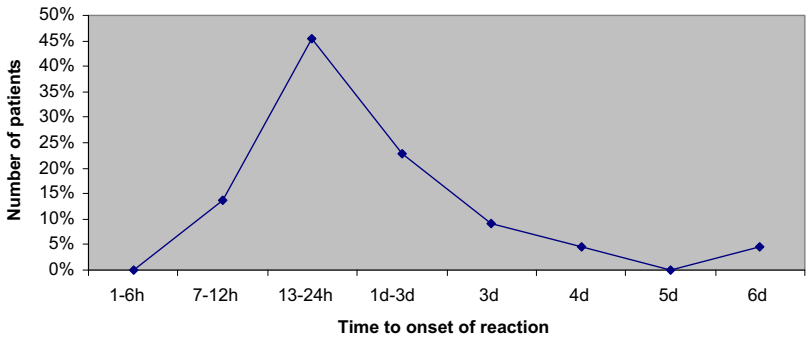

FIG 1. Time to the onset of hypersensitivity reactions.

TABLE I. Results of skin and challenge tests of patients who had positive skin test results

Patient no.	Age (y)	Sex	Positive skin test results: Iodixanol	Positive skin test results: Other ICM: Ionic	Positive skin test results: Other ICM: Nonionic	Well-tolerated challenge with:
3	63	M	IDT + (undiluted, 72 h)	−	−	Iobitridol
6	53	M	IDT + (undiluted, 24 h)	−	Iohexol (IDT, undiluted, 24 h) Iopentol (IDT, undiluted, 24 h) Ioversol (IDT, undiluted, 24 h)	Iobitridol
9	44	F	PT + (96 h)	−	−	Iobitridol
13	54	F	IDT + (undiluted, 24 h) PT + (48 h)	−	Iohexol (IDT, undiluted, 24 h) Iopentol (IDT, undiluted, 24 h)	Iobitridol
14	55	M	IDT + (undiluted, 48 h)	Ioxaglate (IDT, undiluted, 48 h) Ioxitalamate (IDT, undiluted, 48 h)	Iohexol (IDT, undiluted, 48 h) Iomeprol (IDT, undiluted, 48 h) Iopamidol (IDT, undiluted, 48 h) Iopentol (IDT, undiluted, 48 h) Ioversol (IDT, undiluted, 48 h)	Iobitridol
15	58	M	IDT + (10^{-1}, 48 h)	−	Iohexol (IDT, 10^{-1}, 48 h) Ioversol (IDT, 10^{-1}, 48 h)	Iobitridol
16	57	M	IDT + (10^{-1}, 48 h)	−	−	Iobitridol
18	51	F	IDT + (undiluted, 24 h) PT + (48 h)	−	Iohexol (IDT, undiluted, 24 h) Ioversol (PT, 48 h)	Iobitridol
19	59	M	IDT + (10^{-2}, 24 h)	Ioxitalamate (IDT, 10^{-1}, 48 h)	Iomeprol (IDT, undiluted, 48 h) Iopamidol (IDT, undiluted, 24 h)	Iobitridol
20	50	M	IDT + (10^{-1}, 24 h)	−	−	Iobitridol
22	49	M	IDT + (undiluted, 24 h)	Amidotrizoate (IDT, undiluted, 24 h)	Iobitridol (IDT, undiluted, 24 h) Iohexol (IDT, undiluted, 24 h)	Iomeprol

−, Negative results for all test procedures; +, positive test result; *F*, female; *M*, male; *PT*, patch test.

TABLE II. Challenge test results in patients with a delayed hypersensitivity reaction to iodixanol and either a positive or negative skin test result to iodixanol

Challenged with:	Patients with positive skin test results to iodixanol	Patients with negative skin test results to iodixanol
Iobitridol	10	6
Iobitridol + iomeprol		2
Iohexol		1
Iomeprol	1	
Iopamidol		1
Ioversol		1

All challenge test results were negative.

provided guidance to alternative ICM that might be administered to these patients if further ICM-based examinations are required. The choice of iobitridol for 18 challenge tests was guided by the finding that these patients had negative skin test results to this compound and that iobitridol has a quite different chemical structure compared with that of iodixanol. Our study tends to suggest that there might be a putative link between the chemical structure and pattern of cross-reactivity among ICM. This study is the largest to date to have investigated the usefulness of skin testing to select a safe ICM for challenging patients with nonimmediate hypersensitivity reactions to iodixanol.

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